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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,310	11/21/2003	Paul G. Brunetta	PI979R1	3292
9157	7590	06/18/2007	EXAMINER	
GENENTECH, INC.			HUYNH, PHUONG N	
1 DNA WAY			ART UNIT	PAPER NUMBER
SOUTH SAN FRANCISCO, CA 94080			1644	
			MAIL DATE	DELIVERY MODE
			06/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/719,310	Applicant(s) BRUNETTA ET AL.	
	Examiner Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 8-16 and 32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 8-16 and 32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>3/27/07; 1/24/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/07 has been entered.
2. Claims 1-3, 8-16 and 32 are pending and are being acted upon in this Office Action.
3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
4. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
5. Claims 1-3, 8-16, and 32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/15730 publication (of record, March 8, 2001; PTO 1449) in view of WO 98/02540 (of record, January 22, 1998; PTO 1449) and Feldman et al (of record, Dermatol Online J 6(1): 4, September 2000; PTO 892).

The WO 01/15730 publication teaches a method of treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular) by administering to a mammal such as human, dogs, horses, (see abstract, page 14, lines 4-8, in particular) an effective amount of an antibody which binds ErbB2

such as humanized version of 4D5 also known as HERCEPTIN®, 7C2, 7F3, 4D5, 2C4 (see page 33, in particular). The reference monoclonal antibodies such as 7C2, 7F3, 4D5 obviously block the ErbB2 ligand from activating its receptor, ErbB2. The reference humanized version of the antibody 2C4 obviously competes with the monoclonal antibody 2C4 because it contains the same CDRs as the mouse monoclonal antibody 2C4 and binds to the same epitope. The WO 01/15730 publication further teaches the humanized form of 2C4 (see page 5, lines 34, in particular) and antibody fragment thereof such as Fab or Fv (see page 11, lines 26-37, page 12-13, in particular). The reference antibody is not conjugated to with a cytotoxic agent (see page 33, page 14, lines 30-33, claim 1 of WO 01/15730 publication, in particular). The WO 01/15730 publication teaches administering to the patient such as human a second therapeutic agent such as chemotherapeutic agent (see page 14, lines 34-38 through page 15, lines 1-29, in particular), a growth inhibitory agent (see page 15, lines 30 through page 16, lines 1-2, in particular), or anti-ErbB2 or binding fragment thereof conjugated to a cytotoxic agent such as bacterial toxin (see page 25, lines 31-39, page 26, lines 1-11, in particular). The reference antibody is administered at least one dose to the patient in an amount from about 4mg/kg and not exceeding 30mg/kg, which is within the claimed limitation of about 0.5mg/kg to about 30 mg/kg.

The claimed invention differs from the teachings of the reference only in that the method wherein the disease is psoriasis instead of benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders.

The WO 98/02540 publication teaches ErbB2 plays a role in psoriasis and a method of treating psoriasis by administering to the mammal with an agent that blocks the ErbB2 ligand from binding to its receptor ErbB2 such as soluble ErbB2 receptor that comprises extracellular domain of ErbB2 fused to IgG (see page 35, line 11, homodimer, abstract, in particular). The WO 98/02540 publication teaches blocking ErbB2 using ErbB antagonist such as ErbB2 and ErbB3 or ErbB2 and ErbB4 fused to Fc prevents the ErbB ligand from binding and activation of the ErbB receptor (see page 25, lines 1-10, page 23, lines 23-31, heterodimer, abstract, claims 37-40, in particular).

Feldman et al teach a method of treating psoriasis that involved inflammation, hyperproliferation of keratinocyte by administering to the patient various immunosuppressive agent or a combination of such agents such as corticosteroid (steroid), cyclosporine, retinoid, psoralens, coal tar, and phototherapy such as UVB, methotrexate (see entire document, abstract, summary, in particular). Feldman et al teach a combination of modalities can be utilized to

enhance the therapeutic effect and minimize the adverse effects that could result from excessive use of one agent (see Treatment goal, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat psoriasis by substituting the ErbB2-IgG that blocks ErbB2 ligand from binding to ErbB2 as taught by the WO 98/02540 publication for the antibody or Fab that binds to ErbB2 and thereby preventing the binding of ErbB2 ligand to its receptor as taught by the WO 01/15730 publication in combination with a second therapeutic agent such as immunosuppressive agent, chemotherapeutic agent or cytotoxic agent as taught by the WO 01/15730 publication or immunosuppressive agent or anti-inflammatory agent such as corticosteroid (steroid), cyclosporine, retinoid, psoralens, coal tar, and phototherapy such as UVB, methotrexate that are useful for treating psoriasis as taught by Feldman et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because blocking ErbB2 ligand from binding to ErbB2 receptor is useful for treating psoriasis as taught by the WO 98/02540 publication (see page 35, line 11, homodimer, abstract, in particular). The WO 01/15730 publication teaches antibody that binds specifically to ErbB2 is useful for treating hyperproliferative epithelial, inflammatory and angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular). Feldman et al teach a method of treating psoriasis that involved in inflammation and hyperproliferation of keratinocyte by administering to the patient various immunosuppressive agent or a combination of such agents such as corticosteroid, cyclosporine, retinoid, psoralens, coal tar, and phototherapy such as UVB, methotrexate (see entire document, abstract, summary, in particular). Feldman et al teach a combination of modalities can be utilized to enhance the therapeutic effect and minimize the adverse effects that could result from excessive use of one agent (see Treatment goal, in particular).

Applicants' arguments filed 3/28/07 have been fully considered but are not found persuasive.

Applicants' position is that there is insufficient showing why a skilled person, confronted with the same problem as the present inventors and with no knowledge of the claimed invention, would have been motivated as of the effective filing date to select the elements from the cited prior art references for combination in the manner claimed in the present application. In addition, Applicants reiterate their position, expressed in earlier responses, that psoriasis has acquired a

separate place in the art, and thus, the fact that certain inflammatory or immunologic disorders are described to respond to a treatment, does not create a reasonable expectation that psoriasis could be treated in a similar manner. In view of this distinction, one of ordinary skill in the art at the time the present invention was made would not have had any motivation to combine WO 01/15730 and WO 98/02540. Indeed, the only motivation to make the purported combination derives from the disclosure of the present application, and is the result of an impermissible hindsight reconstruction of the claimed invention. Applicants further submit that even if WO 01/15730 and WO 98/02540 could be properly combined, they would still not make obvious the claimed invention. WO 01/157030 was cited for its teaching of the treatment of various non-malignant conditions, in particular inflammatory and immunologic conditions, using ErbB2 antibodies. WO 98/02540 teaches to use of heteromultimeric immunoadhesins, including the extracellular domains of two at least two different ErbB receptors (e.g., ErbB2/ErbB3, ErbB2/ErbB4, ErbB3/ErbB4), to treat psoriasis. At the priority date of the present invention, based on these two disclosures, without the knowledge of the present invention, one of ordinary skill would not have concluded that antibodies, which bind ErbB2 could treat psoriasis with a reasonable expectation of success. Finally, it is emphasized that psoriasis is a chronic disease that is difficult to treat. A reasonable expectation that such treatment is likely to work by following the methods of the present invention has only been created by demonstrating the ability of the antibodies herein to block signaling through the MAP kinase pathway, the activation of which was, in turn, known to be responsible for epidermal hyperproliferation in psoriasis (see, e.g. Haase et al., supra).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

In contrast to applicants' assertion that there is no reasonable expectation of success that psoriasis could be treated in a similar manner as treating proliferative cancer cell, it is well known to one of ordinary skill in the immunology art at the time the invention was filed that ErbB2 plays a role in psoriasis (see WO 98/02540 publication page 35, line 11, homodimer, abstract, in

particular). It is also known to one of ordinary skill in the immunology art at the time the invention was filed that ErbB2 plays a role in a benign hyperproliferative *epithelial, inflammatory* angiogenic immunological disorders (see WO 01/15730 publication, page 14, lines 9-14, page 30, lines 31-38, in particular). The teachings of WO 01/15730 publication pertaining to the success in treating psoriasis using ErbB2 antagonist such as soluble ErbB2 receptor (ErbB2-Fc) and the teachings of WO 01/15730 publication indicating success in treating benign hyperproliferative *epithelial, inflammatory* angiogenic immunological disorders using ErbB2 antagonist such as antibody that binds to ErbB2 in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In response to applicants' argument that psoriasis is a chronic disease that is difficult to treat and the present invention has only been created by demonstrating the ability of the antibodies herein to block signaling through the MAP kinase pathway, the activation of which was, in turn, known to be responsible for epidermal hyperproliferation in psoriasis (see, e.g. Haase et al., supra), it is noted that none of the claims recite antibody that binds to ErbB2 block ErbB2 signaling through the MAP kinase pathway. Further, there is no evidence in the specification as filed that treating a human patient with psoriasis with any antibody which binds ErbB2 such as antibody that binds to the same epitope in the extracellular domain of ErbB2 as that bound by monoclonal antibody 2C4 or humanized 2C4 or monoclonal antibody 2C4 inhibits MAP kinase pathway in human. The specification merely discloses treating MCF cells *in vitro* with monoclonal antibody 2C4 blocks EGF, TNF- α and HRG stimulated MAPK activation, see page 51 and Figure 10. These MCF cells are human breast cancer cells and they are not even keratinocytes as discussed in Haase et al reference.

6. New objection and Rejections:

7. Claim 32 is objected to because "Ethanercept" is misspelled. It should have been "Etanercept".

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8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 15 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for therapeutic treatment of psoriasis in a human as set forth in claims 1-3, 8-14, and 16, **does not** reasonably provide enablement for a method for therapeutic treatment of psoriasis in a human using any EGFR-targeted drug, any steroid, any antibody that binds to B-cell surface antigen, any TNF antagonist, any IL-1 antagonist, any IL-10 agonist in combination with an antibody which binds to ErbB2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification does not teach how to use any steroid other than glucocorticosteroid, prednisone, methylprednisolone, or any cytokine, any antibody that binds to B-cell surface antigen other than CD19, CD20 and CD22, any IL-1 antagonist other than Kineret from Amgen, any TNF antagonist, any IL-10 agonist, any EGFR-target drug other than antibody that binds to EGFR in combination with any antibody which binds ErbB2 for the claimed method for the therapeutic treatment of psoriasis in human.

The specification discloses only four monoclonal antibodies that bind specifically to human ErbB2 such as 7C2, 7F3, 4D5, and 2C4 produced by hybridomas under the ATCC accession number ATCC HB-12215, ATCC HB-12216, ATCC CRL 10463 and ATCC HB-12697, respective (page 44). The specification discloses humanized antibodies and binding fragment thereof (see pages 45, 8-11 and page 48). The specification further teaches the antibody such as 2C4 inhibits the association of ErbB2 and ErbB3 in mammary tumor cell lines MCF7 and

SK-BR3 (see page 47). The specification further discloses that binding of monoclonal antibody 2C4 to human erbB2 blocks EGF, TGF α or HRG mediated activation of MAPK kinase in MCF7 cancer cells (see page 51). The specification asserts that that any non-malignant disease, any disorder including psoriasis *may be treated* with anti-ErbB2 antibody alone or co-administration of adjunct therapy (see page 53, lines 6-24, in particular). The specification at page 15 defines the term "treatment" referring to both therapeutic treatment and "prophylactic" or "preventive" measures. The specification does not teach any vitro assay that is predictive of preventing psoriasis in all mammals in vivo by administration of any antibody that binds to any ErbB2.

The specification does not teach the use of any steroid other than glucocorticosteroid, prednisone, methyprednisolone in combination with any antibody which binds ErbB2 for treating psoriasis in human.

As evidenced by the teachings of O'driscoll et al (Clin Exp Dermatol 15(1): 68-69, Jan 1990; PTO 892), steroid treatment such as estradiol-testosterone implant exacerbated psoriasis and the rash did not resolve until the effects of the implant had worn off and recurred following insertion of a second estradiol-testosterone implant (see abstract, in particular). Given the numerous steroids as encompassed by the claims in combination with any anti-ErbB2 antibody, there is insufficient guidance and *in vivo* working example showing any combination of such treatment is effective for therapy of psoriasis, a chronic disease with no known cure, even after effective filing date of this application. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention.

With respect to the use of a combination of any cytokine with any antibody which binds ErbB2 for the claimed method, the specification does not teach the use of any cytokine other than IL10 in combination with antibody which binds ErbB2 for treating psoriasis.

As evidenced by the teachings of Kelly et al (Br J Dermatology 128(4):468-9, April 1993; PTO 892), Kelly et al teach treating patient with cytokine such as GM-CSF exacerbate psoriasis (see abstract, in particular).

Likewise, Ladoyanni et al teach interferon alpha treatment can exacerbate existing psoriasis and induce de novo psoriasis and psoriatic arthritis (see abstract, in particular). Given the numerous cytokine as encompassed by the claims, there is insufficient guidance and *in vivo* working example showing any combination of such treatment is effective for therapy of psoriasis, a chronic disease with no known cure, even after effective filing date of this application.

Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention.

With respect to the use of any antibody that binds to B-cell surface antigen other than CD19, CD20 and CD22, there is insufficient guidance as to the binding specificity of such antibody, let alone a combination with all antibody that binds to ErbB2 for treating human patient with psoriasis.

With respect to the use of any TNF antagonist, the state of the art as exemplified by the teachings of Kary et al (Ann Rheuma Dis 65: 405-407, 2006; PTO 892) is such that patient treated with etanercept for rheumatoid arthritis lead to either a new onset or an exacerbation of psoriatic skin lesions during anti-TNF α treatment (see entire document, page 406, in particular).

Shear et al (Drug Saf 29(1): 49-66, 2006; PTO 892) teach Information on the safety of biological agents in inflammatory conditions such as rheumatoid arthritis and Crohn's disease can not be directly extrapolated to psoriasis. An increased incidence of lymphomas has been postulated to be associated with etanercept, infliximab and adalimumab; serious infections, such as tuberculosis, have also been reported with these three biologicals, all of which target TNF-alpha. Demyelinating disorders, such as multiple sclerosis, have been reported with some biologicals as has congestive heart failure. Alefacept, because of its mechanism of action of lowering the number of active T cells, is associated with low T cell counts. Efalizumab has been associated with thrombocytopenia and haemolytic anaemia. Data on the safety of >2.5 years' continuous treatment with efalizumab are reassuring and a valuable beginning to understanding the role and risk of harm of long-term therapy for a chronic disease.

With respect to the use of any IL-1 antagonist other than Kineret, any IL-10 agonist, and any EGFR-target drug other than antibody that binds to EGFR, the claims encompassed any and all IL-1 antagonist, IL-10 agonist, and all EGFR-target drug.

The specification discloses only one IL-10 antagonist. Other than Kineret, the specification does not teach the structure of any IL-10 antagonist for the claimed method. The specification does not teach any assays that is useful for screening IL-10 antagonist and is predictive of success in vivo. Likewise, there is insufficient guidance as to the structure of any IL-10 agonist other than the IL-10 itself, and any EGFR-target drug other than antibody that binds to EGFR. There is a lack of *in vivo* working example showing that any undisclosed IL-10 antagonist, IL-1 agonist or any drug directed toward EGFR alone is effective for treating psoriasis, let alone a combination of any antibody that binds to ErbB2. Until the structure of such

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IL-1 antagonist, IL-10 agonist and EGFR-target drug have been disclosed, the specification merely extends an invitation to one skilled in the art to come with the structure of such agent and then test each to see whether such agent is useful for the claimed method.

Ngo et al, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495).

Sauder et al, of record, teach psoriasis is a chronic T cell mediated inflammatory skin disease and no cure for psoriasis has ever been found (see page 206, col. 2, in particular). Sauder further teach the traditional options for psoriasis involves in the use of both topical and systemic medications such as topical corticosteroid, coal tar, salicylic acid, vitamin D derivative, phototherapy, methotrexate, or cyclosporine (see page 207-208, in particular).

Giaccone et al, of record, teach predicting the future for patients using EGF receptor targeted agent is unpredictable and further research is required before the optimal dosing strategy for HER1/EGFR tyrosine kinase inhibitor (see entire documents, abstract, in particular).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 15 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any steroid, (2) any antibody that binds to B-cell surface antigen, (3) any EGFR-targeted drug, (4) any IL-1

antagonist, and (5) any IL-10 agonist in combination with an antibody which binds to ErbB2 for the claimed method.

The specification discloses four monoclonal antibodies that bind specifically to human ErbB2 such as 7C2, 7F3, 4D5, and 2C4 produced by hybridomas under the ATCC accession number ATCC HB-12215, ATCC HB-12216, ATCC CRL 10463 and ATCC HB-12697, respective (page 44). The specification discloses humanized antibodies and binding fragment thereof (see pages 45, 8-11 and page 48). The specification further teaches the antibody such as 2C4 inhibits the association of ErbB2 and ErbB3 in mammary tumor cell lines MCF7 and SK-BR3 (see page 47). The specification further discloses that binding of monoclonal antibody 2C4 to human erbB2 blocks EGF, TGF α or HRG mediated activation of MAPK kinase in MCF7 cancer cells (see page 51). The specification asserts that that any non-malignant disease, any disorder including psoriasis *may be treated* with anti-ErbB2 antibody alone or co-administration of adjunct therapy (see page 53, lines 6-24, in particular). The specification at page 15 defines the term "treatment" referring to both therapeutic treatment and "prophylactic" or "preventive" measures. The specification does not teach any vitro assay that is predictive of preventing psoriasis in all mammals in vivo by administration of any antibody that binds to any ErbB2.

The specification does not adequately describe the use of any steroid other than glucocorticosteroid, prednisone, methyprednisolone in combination with any antibody which binds ErbB2 for treating psoriasis in human.

As evidenced by the teachings of O'driscoll et al (Clin Exp Dermatol 15(1): 68-69, Jan 1990; PTO 892), steroid treatment such as estradiol-testosterone implant exacerbated psoriasis and the rash did not resolve until the effects of the implant had worn off and recurred following insertion of a second estradiol-testosterone implant (see abstract, in particular).

Other than glucocorticosteroid, prednisone, methyprednisolone in combination with any antibody which binds ErbB2 for treating psoriasis in human, all other steroid for use in combination with antibody that binds to ErbB2 are not adequately described.

With respect to the use of a combination of any cytokine with any antibody which binds ErbB2 for the claimed method, there is no disclosure of any cytokine other than IL10 in combination with antibody which binds ErbB2 for treating psoriasis.

As evidenced by the teachings of Kelly et al (Br J Dermatology 128(4): 468-9, April 1993; PTO 892), Kelly et al teach treating patient with cytokine such as GM-CSF exacerbate psoriasis (see abstract, in particular).

Likewise, Ladoyanni et al (J Drugs in Dermatology 4(2): 221-222, 2005; PTO 892) teach interferon alpha treatment can exacerbate existing psoriasis and induce de novo psoriasis and psoriatic arthritis (see abstract, in particular). Given the numerous cytokine as encompassed by the claims, all cytokines other than IL10 for the claimed method are not adequately described.

With respect to the use of any antibody that binds to B-cell surface antigen other than CD19, CD20 and CD22, the binding specificity of such antibody to which antigen on B cell for the claimed method is not adequately described.

With respect to the use of any IL-1 antagonist, the specification discloses only Kineret as the IL-1 antagonist. One species hardly constitutes a genus for the claimed method.

Likewise, there is insufficient disclosure about the structure of such IL-10 agonist and EGFR-target drug without the chemical structure. The specification discloses only IL-10 as the agonist and only antibody that binds EGFR as EGFR-target drug. As such, the specification merely extends an invitation to one skilled in the art to come with the structure of such agonist or EGFR-target drug for the claimed method.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of steroid, antibody that binds to B-cell surface antigen, EGFR-targeted drug, IL-1 antagonist, and IL-10 agonist in combination with an antibody which binds to ErbB2 for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
12. Claims 2 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "antibody blocks ligand activation of an **ErbB receptor**" in claim 2 has antecedent basis in base claim 1 because the antibody in claim 1 binds to **ErbB2** receptor should block ligand activation of ErbB2 receptor, and not just any ErbB receptor.

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The recitation of "D2E7" and "CDP-870" in claim 32 is ambiguous and indefinite because "D2E7" and "CDP-870" are merely laboratory designations which do not clearly define the products in the claimed method, since different laboratories may use the same laboratory designations to define completely distinct products.

The recitation of "TNF antagonist", "Etanercept", "IL-1 antagonist" and "Kineret" in claim 32 is in improper Markush language. This is because "Etanercept" is a TNF antagonist while Kineret is an IL-1 antagonist.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-3, 8-16, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/15730 publication (of record, March 8, 2001; PTO 1449) in view of US Pat 5,650,415 (issued July 22, 1997; PTO 892).

The WO 01/15730 publication teaches a method of treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular) by administering to a mammal such as human (see abstract, page 14, lines 4-8, in particular) an effective amount of an antibody which binds ErbB2 such as humanized version of 4D5 also known as HERCEPTIN®, 7C2, 7F3, 4D5, 2C4 (see page 33, in particular). The reference monoclonal antibodies such as 7C2, 7F3, 4D5 obviously block the ErbB2 ligand from activating the ErbB2 receptor because these antibodies bind to the extracellular domain of

ErbB2. The WO 01/15730 publication further teaches the humanized form of 2C4 (see page 5, lines 34, in particular) and antibody fragment thereof such as Fab or Fv (see page 11, lines 26-37, page 12-13, in particular). The reference humanized version of the antibody 2C4 or Fab fragment inherently competes with the monoclonal antibody 2C4 because it contains the same CDRs as the mouse monoclonal antibody 2C4 and binds to the same epitope as monoclonal antibody 2C4. The reference antibody is not conjugated to with a cytotoxic agent (see page 33, page 14, lines 30-33, claim 1 of WO 01/15730 publication, in particular). The WO 01/15730 publication teaches administering to the patient such as human a second therapeutic agent such as chemotherapeutic agent (see page 14, lines 34-38 through page 15, lines 1-29, in particular), a growth inhibitory agent (see page 15, lines 30 through page 16, lines 1-2, in particular), or anti-ErbB2 or binding fragment thereof conjugated to a cytotoxic agent such as bacterial toxin (see page 25, lines 31-39, page 26, lines 1-11, in particular). The reference antibody is administered at least one dose to the patient in an amount from about 4mg/kg and not exceeding 30mg/kg, which is within the claimed limitation of about 0.5mg/kg to about 30 mg/kg.

The claimed invention differs from the teachings of the reference only in that the method for therapeutic treatment of psoriasis instead of benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders.

The invention in claims 15 and 32 differ from the teachings of the reference only in that the method further comprising administering to the human a therapeutically effective amount of a tyrosine kinase inhibitor.

The '415 patent teaches that tyrosine kinase includes HER family such as EGFR, HER2, HER3 and HER4, and many of these kinases have been found to be involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc (see col. 1, lines 24-41, in particular). The '415 patent teaches that various tyrosine kinase inhibitors such as the compounds as shown in the Summary of the Invention are useful for treating various cell proliferative disorders involving HER2 such as cancers and psoriasis (see summary of invention, claims 2-3 and 8 of the '415 patent, in particular). The '415 patent further teaches compounds show to have good effect against HER2 are likely to also have good effect against other members of the Her family (see col. 3, line 18-32, col. 4, lines 40-45, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat psoriasis by either substituting and/or combining the tyrosine kinase inhibitor that inhibit HER2 cellular signaling pathways as taught by the '415 patent for the

antibody or binding fragment thereof which binds to ErbB2 that is useful for treating benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders as taught by the WO 01/15730 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success in combining the HER2 tyrosine kinase inhibitor with the anti-ErbB2 antibody to treat psoriasis because many HER2 family of tyrosine kinases have been found to be involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc (see col. 1, lines 24-41, in particular) and tyrosine kinase inhibitor inhibits cellular tyrosine kinase signaling in psoriasis (see col. 3, line 18-32, col. 4, lines 41-45, in particular). One having ordinary skill in the art would have been motivated with the expectation of success in substituting the ErbB2 (HER2) tyrosine kinase inhibitor useful for treating psoriasis as taught by the '415 patent for the antibody because the '415 patent teaches compounds show to have good effect against HER2 are likely to also have good effect against other members of the Her family (see col. 3, line 18-32, col. 4, lines 40-45, in particular). The WO 01/15730 publication teaches antibody which binds to ErbB2 alone or conjugated antibody that binds to ErbB2 is useful for treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular).

16. Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/15730 publication (of record, March 8, 2001; PTO 1449) in view of US Pat 5,650,415 (issued July 22, 1997; PTO 892) and US Pat No 5,783,186 (issued July 21, 1998; PTO 892).

The WO 01/15730 publication teaches a method of treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular) by administering to a mammal such as human (see abstract, page 14, lines 4-8, in particular) an effective amount of an antibody which binds ErbB2 such as humanized version of 4D5 also known as HERCEPTIN®, 7C2, 7F3, 4D5, 2C4 (see page 33, in particular). The reference monoclonal antibodies such as 7C2, 7F3, 4D5 obviously block the ErbB2 ligand from activating its receptor, ErbB2. The reference humanized version of the antibody 2C4 obviously competes with the monoclonal antibody 2C4 because it contains the same CDRs as the mouse monoclonal antibody 2C4 and binds to the same epitope. The WO 01/15730 publication

further teaches the humanized form of 2C4 (see page 5, lines 34, in particular) and antibody fragment thereof such as Fab or Fv (see page 11, lines 26-37, page 12-13, in particular). The reference antibody is not conjugated to with a cytotoxic agent (see page 33, page 14, lines 30-33, claim 1 of WO 01/15730 publication, in particular). The WO 01/15730 publication teaches administering to the patient such as human a second therapeutic agent such as chemotherapeutic agent (see page 14, lines 34-38 through page 15, lines 1-29, in particular), a growth inhibitory agent (see page 15, lines 30 through page 16, lines 1-2, in particular), or anti-ErbB2 or binding fragment thereof conjugated to a cytotoxic agent such as bacterial toxin (see page 25, lines 31-39, page 26, lines 1-11, in particular). The reference antibody is administered at least one dose to the patient in an amount from about 4mg/kg and not exceeding 30mg/kg, which is within the claimed limitation of about 0.5mg/kg to about 30 mg/kg.

The claimed invention differs from the teachings of the reference only in that the method wherein the disease is psoriasis instead of benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders.

The invention in claim 15 differ from the teachings of the reference only in that the method further comprising administering to the human another ErbB antibody.

The '415 patent teaches tyrosine kinases includes HER family such as EGFR, HER2, HER3 and HER4, and many of these kinases have been found to be involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc (see col. 1, lines 24-41, in particular). The '415 patent further teaches that any compounds show to have good effect against HER2 are likely to also have good effect against other members of the Her family (see col. 3, line 18-32, col. 4, lines 40-45, in particular).

The '186 patent teaches anti-Her2 antibody (also known as HER2 antibody) such as mAb74 and binding fragment thereof that induces apoptosis of cells expressing Her2 receptor and tag Her2 overexpressing cells for elimination by the host immune system (see entire document, abstract, col. 4, lines 36-46, in particular). The '186 patent teaches the advantage of the reference antibody is that the antibody itself is toxic to Her2 expressing cells and reduces some of the undesirable side effect associated with high dose of cytotoxic agents and cell necrosis induced by such agents (see col. 2, lines 46-55, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the Her2 (ErbB2) antibody that induces apoptosis as taught by the '186 patent with any one of the antibody that binds ErbB2 as taught by the WO 01/15730

publication for treating psoriasis by inhibiting the HER family such as EGFR, HER2, HER3 and HER4 kinases that have been found to be involved in pathogenic conditions such as cancer, psoriasis as taught by the '415 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success in treating psoriasis as taught by the '415 patent by combining another ErbB2 antibody that induces apoptosis as taught by the '186 patent with the ErbB2 antibody as taught by the WO 01/15730 publication that is useful for treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders because the '186 patent teaches the advantage of the reference antibody is that the antibody itself is toxic to Her2 expressing cells and the combination with other agent could reduce some of the undesirable side effect associated with high dose of cytotoxic agents and cell necrosis induced by such agents (see col. 2, lines 46-55, in particular). The '415 patent teaches that compounds show to have good effect against HER2 are likely to also have good effect against other members of the Her family (see col. 3, line 18-32, col. 4, lines 40-45, in particular).

17. Claims 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/15730 publication (of record, March 8, 2001; PTO 1449) in view of US Pat 5,650,415 (issued July 22, 1997; PTO 892) and Feldman et al (of record, Dermatol Online J 6(1): 4, September 2000; PTO 892).

The WO 01/15730 publication teaches a method of treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular) by administering to a mammal such as human (see abstract, page 14, lines 4-8, in particular) an effective amount of an antibody which binds ErbB2 such as humanized version of 4D5 also known as HERCEPTIN®, 7C2, 7F3, 4D5, 2C4 (see page 33, in particular). The reference monoclonal antibodies such as 7C2, 7F3, 4D5 obviously block the ErbB2 ligand from activating the ErbB2 receptor because these antibodies bind to the extracellular domain of ErbB2. The WO 01/15730 publication further teaches the humanized form of 2C4 (see page 5, lines 34, in particular) and antibody fragment thereof such as Fab or Fv (see page 11, lines 26-37, page 12-13, in particular). The reference humanized version of the antibody 2C4 or Fab fragment inherently competes with the monoclonal antibody 2C4 because it contains the same CDRs as the

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mouse monoclonal antibody 2C4 and binds to the same epitope as monoclonal antibody 2C4. The reference antibody is not conjugated to with a cytotoxic agent (see page 33, page 14, lines 30-33, claim 1 of WO 01/15730 publication, in particular). The WO 01/15730 publication teaches administering to the patient such as human a second therapeutic agent such as chemotherapeutic agent (see page 14, lines 34-38 through page 15, lines 1-29, in particular), a growth inhibitory agent (see page 15, lines 30 through page 16, lines 1-2, in particular), or anti-ErbB2 or binding fragment thereof conjugated to a cytotoxic agent such as bacterial toxin (see page 25, lines 31-39, page 26, lines 1-11, in particular). The reference antibody is administered at least one dose to the patient in an amount from about 4mg/kg and not exceeding 30mg/kg, which is within the claimed limitation of about 0.5mg/kg to about 30 mg/kg.

The claimed invention differs from the teachings of the reference only in that the method for therapeutic treatment of psoriasis instead of benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders.

The invention in claim 32 differs from the teachings of the reference only in that the method further comprising administering to the human a therapeutically effective amount of a tyrosine kinase inhibitor.

The '415 patent teaches that tyrosine kinase includes HER family such as EGFR, HER2, HER3 and HER4, and many of these kinases have been found to be involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc (see col. 1, lines 24-41, in particular). The '415 patent teaches that various tyrosine kinase inhibitors such as the compounds as shown in the Summary of the Invention are useful for treating various cell proliferative disorders involving HER2 such as cancers and psoriasis (see summary of invention, claims 2-3 and 8 of the '415 patent, in particular). The '415 patent further teaches compounds show to have good effect against HER2 are likely to also have good effect against other members of the Her family (see col. 3, line 18-32, col. 4, lines 40-45, in particular).

Feldman et al teach a method of treating psoriasis that involved inflammation, hyperproliferation of keratinocyte by administering to the patient various immunosuppressive agent or a combination of such agents such as corticosteroid (steroid), cyclosporine, retinoid, psoralens, coal tar, and phototherapy such as UVB, methotrexate (see entire document, abstract, summary, in particular). Feldman et al teach a combination of modalities can be utilized to enhance the therapeutic effect and minimize the adverse effects that could result from excessive use of one agent (see Treatment goal, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made treat psoriasis as taught by the '145 patent by combining any one of the antibody that binds ErbB2 as taught by the WO 01/15730 publication with any one of the agent such as corticosteroid (steroid), cyclosporine, retinoid, psoralens, coal tar, and phototherapy such as UVB, or methotrexate that are well known in the art for treating psoriasis as taught by Feldman et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success in treating psoriasis by combining various agent known in the art as taught by Feldman et al because Feldman et al teach that a combination of modalities can enhance the therapeutic effect and minimize the adverse effects that could result from excessive use of one agent (see Treatment goal, in particular). The '415 patent teaches many HER2 family of tyrosine kinases have been found to be involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc (see col. 1, lines 24-41, in particular) and any compounds that show to have good effect against HER2 are likely to also have good effect against other members of the Her family (see col. 3, line 18-32, col. 4, lines 40-45, in particular). The WO 01/15730 publication teaches antibody which binds to ErbB2 alone or conjugated antibody that binds to ErbB2 is useful for treating a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders (see page 14, lines 9-14, page 30, lines 31-38, in particular).

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.
19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Patent Examiner

Technology Center 1600

June 8, 2007